Functional anatomy of intrinsic alertness: evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere

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Abstract

Alertness, the most basic intensity aspect of attention, probably is a prerequisite for the more complex and capacity demanding domains of attention selectivity. Behaviorally, intrinsic alertness represents the internal (cognitive) control of wakefulness and arousal; typical tasks to assess optimal levels of intrinsic alertness are simple reaction time measurements without preceding warning stimuli. Up until now only parts of the cerebral network subserving alertness have been revealed in animal, lesion, and functional imaging studies. Here, in a ^{15}O-butanol PET activation study in 15 right-handed young healthy male volunteers for this basic attention function we found an extended right hemisphere network including frontal (anterior cingulate–dorsolateral cortical)–inferior parietal–thalamic (pulvinar and possibly the reticular nucleus) and brainstem (ponto-mesencephalic tegmentum, possibly involving the locus coeruleus) structures, when subjects waited for and rapidly responded to a centrally presented white dot by pressing a response key with the right-hand thumb.

Keywords: Intrinsic alertness; Sustained attention; RT measures; PET-functional imaging

1. Introduction

In accordance with van Zomeren and Brouwer [48] attention can be subdivided into two subsystems, one representing the intensity aspects alertness and sustained attention and the other one the selectivity aspects of focused and divided attention. Since intensity aspects are probably a prerequisite of the more complex and capacity demanding domains of attention selectivity [43] we were especially interested in the assessment of neural networks involved in the most basic intensity aspect, namely alertness.

A typical task for the assessment of alertness in the sense of a general level of response readiness [27] is a simple reaction time (RT) measurement. Phasic alertness—i.e., the ability to increase response readiness by external cues—is called for in reaction time tasks in which a warning stimulus precedes the target stimulus [28]. If, however, one is interested in the examination of an optimal activation of intrinsic attentional resources, the measurement of RT without an external warning is most appropriate.

The distinction between intrinsic, non-phasic activation of alertness and sustained attention, however, is not clearcut in the PET-literature although it has been given in taxonomies of attention [31, 42, 48]. Some authors have defined even short periods of endogeneously maintaining vigilant responding as sustained attention ([34]; other references given there). In our view, however, the distinction between this notion of sustained attention and alerting without warning stimuli lies in the fact that sustained attention tasks usually do not focus on speed of response as alerting tasks typically do. Rather, subjects have to monitor (frequent) occurrences of a certain stimulus [36]. The total number of hits and misses for these stimuli is taken as the primary dependent variable. Thus, sustained attention tasks in contrast to alerting RT measurements probably do not necessarily provoke an optimal level of brainstem activation which was, however, shown in a study by Kinomura et al. [14] in which subjects had to respond rapidly and in which response times were registered.

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Lesion studies in stroke patients revealed an important role of the right hemisphere for alertness; e.g., Howes and Boller [13] as well as Posner et al. [29] and Ladavas [15] have reported a dramatic increase in simple visual and auditory RT after RH-lesions. The observation that RH patients nevertheless can profit from a warning stimulus [29] shows that it is the intrinsic and not the phasic aspect of alertness which is impaired after lesions of the right hemisphere.

According to Posner and Petersen [30], the role of noradrenergic (NA) pathways in alerting may lie, in particular, in providing an adequate level of arousal. From lesion studies in rats [37–39] there is evidence for a right hemisphere (RH) bias in the NA system, originating in the locus coeruleus and projecting most strongly to frontal areas. These studies lend support to the hypothesis that there also exists top-down regulation of this NA activation by the right frontal cortex since lesions in this area led to a significant decrease of NA in both hemispheres and in the locus coeruleus. In a PET study looking for the effects of clonidine, an α2-adrenoceptor agonist and noradrenaline antagonist [8] on the activation during a rapid visual information processing task, the authors found a decrease of activation in the right thalamus and bilaterally in the superior frontal and inferior parietal cortex but an increase in the right anterior cingulate. It seems that under the influence of clonidine the subjects needed more effort to cope with the demands of the cognitive tasks, which might call for a higher internal, cognitive control of arousal.

According to Fernandez-Duque and Posner [10] the alerting network seems to co-activate, either directly or via the brainstem, the posterior attention system in the parietal cortex involved in spatial orienting of attention [30].

PET- [3, 24] and fMRI- studies [18] of sustained attention in normal subjects using tasks without RT measurements and lasting for short periods (40 s) have revealed a fronto-parietal RH network for the auditory, visual and somatosensory stimulus modality. Coull et al. [6] in another PET study used a rapid visual information processing task, which they describe as a test of sustained attention, also requiring working memory and selective attention for its successful execution. Subjects had to monitor sequences of digits (100 or 200 per min) and were asked to press a mouse key in response to target sequences, but no RTs were reported. Compared with a rest condition, the task revealed bilateral activation in the inferior frontal gyri, parietal cortex and fusiform gyrus as well as in the right frontal superior gyrus rostrally. In comparison with a simple sustained attention control condition, the right frontal activation was no longer present. These results, too, corroborate the assumption of a right fronto-parietal network for simple sustained attention tasks, whereas for more complex tasks also comprising aspects of working memory and selective attention an additional involvement of left hemisphere frontal and parietal structures could be demonstrated (see also [4]).

Paus et al. [25] studied PET-activation for an auditory vigilance task which lasted for 60 min with very infrequent target stimuli, thus representing a classical vigilance paradigm in the sense of Mackworth [19]. In contrast to most other studies on sustained attention, subjects had to respond as fast as possible to the very infrequent auditory target stimuli which appeared at a rate of about 1 per min. The authors found an increase in reaction time and of θ-activity in the EEG over time which correlated with activation decreases of the thalamus, the right ventrolateral and dorsolateral frontal cortex, the parietal and the temporal cortex. Activation of the thalamus co-varied with activation of the right ponto-mesencephalic tegmentum, the anterior cingulate and the substantia innominata. Coull [6] summarized similar results from another PET-study on sustained attention for the cortical and thalamic structures. Again, the specific role of the right frontal and parietal cortex in sustained attention was pointed out. The fact that activation in these two areas only decreased over time for a non-selective attention task, but not for a selective one was interpreted as a functional modulation of selective by sustained attention.

In the PET-study by Kinomura et al. [14] which explicitly addresses activation of alertness, an involvement of thalamic and brainstem (mesencephalic tegmentum) structures in simple visual as well as somatosensory RT tasks was revealed. The authors, however, only reported a region of interest analysis for thalamus and brainstem and did not provide information on cortical activation.

Up to now in the visual modality, only subcortical *or* right hemisphere cortical brain regions subserving intrinsic regulation of alertness *or* sustained attention have been revealed in functional imaging and animal studies although a more extended cortico-subcortical network for intensity aspects of attention might be hypothesized, as has been demonstrated for the auditory modality in a vigilance task by means of long duration reaction time measurements [25]. Therefore, a simple centrally presented visual reaction time paradigm without warning stimulus was chosen for our study, just like in the PET-study by Kinomura et al. [14]. With such a simple reaction time task, aspects both of short term visual sustained attention (detection of target stimuli as proposed in Robertson et al. [34]) and optimal intrinsic alerting by asking for fast responses [27, 48] are combined, at the same time avoiding involvement of selective attention or working memory. We chose a long interstimulus interval of 3–5 s, making it very unlikely that a preceding reaction stimulus can act as a warning for the subsequent stimulus, which would change the task into a phasic alertness task. Lansing et al. [17] in an EEG study have shown that a warning

stimulus leads to an optimal preactivation if presented 0.6–1 s before the stimulus which has to be responded to.

2. Material and methods

2.1. Subjects

A total of 15 healthy, right-handed (according to a German translation of the Oldfield [23] handedness inventory) male volunteers (median age = 27 years, range = 23–34 years) with no history of neurological or psychiatric illness took part in the study which was approved by the ethical committee and federal authorities. All were students of the Technical University of Aachen. All subjects gave informed, written consent and were paid for participation in the study.

2.2. Task

There were two different tasks, each of which had to be carried out twice:

(1) Alertness: rapid right-hand thumb responses (key presses) to a white light spot (diameter 18 mm) irregularly (frequency of 1 per 3–5 s) appearing centrally at the location of a small square serving as a fixation point on a 17″ black monitor screen, which was mounted at a distance of 50 cm from the subject's head.
(2) Sensorimotor control for the purely sensory and motor aspects of the alertness condition: key presses at a self-determined rate (about 1 per s) while looking at the central white light spot used for the alertness task now flickering at a rate just below the individual flicker fusion frequency. The high flicker frequency was required in order to prevent another alertness task since under this condition subjects are unable to synchronize their key presses with the flicker frequency of the white light. The high frequency of thumb presses was necessary to ensure automatized motor actions without aspects of cognitive control. Thus, it proved impossible to provide a sensorimotor control condition which was more parallel to the alertness condition with respect to the frequency of the stimulus and of the motor response.

During all conditions subjects placed their right hand on an arm rest and held their right-hand thumb attached to a 5×5 cm response key. The median reaction time to the white light spot was 192 ms (range = 153–267), which is a normal performance in healthy young subjects.

We had also included another condition which, however, is irrelevant for the study of alertness. Therefore it was not analysed any further and will not be reported on. Each condition lasted for 60 s and was given twice in counterbalanced order.

2.3. Positron emission computed tomography scanning

Scans of rCBF were obtained for each subject using a GE PC4096 Plus scanner which provides 15 transverse sections through the brain spaced 6.5 mm apart (center to center). Transmission scans performed with a ^{68}Ge rotating line source were used for measured attenuation correction. A laser positioning system helped to obtain images with the most caudal plane 27 mm above and parallel to the canthomeatal line. Emission scans were recorded after the intravenous bolus administration of 1500 MBq ^{15}O-butanol (half-life 123 s). List mode acquisition of data for all 15 slices was started simultaneously with the injection. This data was framed into a single time frame of 40 s starting at the tracer's entry into the brain. Using filtered backprojection the reconstructed image resolution was about 9 mm full width at half maximum. The activity images were not further quantified and regarded as estimates of rCBF. The time interval between scans was about 12 min; the total examination time per subject was about 2 h including preparation. Each subject underwent six PET scans within a single session (maximum radiation dose 5.2 mSv per subject) and a magnetic resonance imaging scan on a different day. During each of the six trials the task began approximately 30 s before injection.

2.4. Data analysis

Images were analysed using Statistical Parametric Maps (SPM96; [11, 12]) implemented in MATLAB (Mathworks Inc., Sherborn, MA, U.S.A.) and run on a SPARC-20 workstation (SUN Microsystems Inc.). Reconstructed PET-data sets were converted to the ANALYZE-format [32] for further processing with SPM96. Each of the 6 PET-images for a subject was automatically realigned and reoriented along the bi-commissural line using a PET-template, in order to correct for head movements between scans. Each reconstructed ^{15}O-butanol scan was subsequently normalized into the standard stereotactic anatomical space of the atlas by Talairach and Tournoux [45] to allow for pixel-by-pixel averaging across subjects. In standard space one voxel represents $2 \times 2 \times 4$ mm in the x, y, and z dimensions, respectively [11]. All images were then smoothed using a Gaussian filter of $15 \times 15 \times 15$ mm to accommodate intersubject variation in brain anatomy and to increase the signal-to-noise ratio in the images.

Analysis of covariance (ANCOVA) was used to eliminate confounding effects of differences in global activity within and between subjects [12]. Areas of significant changes in brain activity between two experimental task conditions, as specified by appropriately weighted linear contrasts, were determined using the t-statistic on a pixel-by-pixel basis. The set of t-values for a linear contrast was transformed to z-values via a probability transformation.

In addition, for each subject the (anatomical) MRI scan was co-registered to the PET brain space, normalized and averaged across subjects to yield an averaged co-registered MRI template on which the group PET data were superimposed.

We report exclusively on the comparison between the alertness and the sensorimotor control condition, since only for this comparison were sensory and motor aspects of the alertness activation controlled.

3. Results

3.1. Changes in rCBF

Results of the SPM96 comparison between the alertness and the combined control condition are depicted in the three SPM{Z} two-dimensional projections of Fig. 1. Brain areas showing significant changes in rCBF between both conditions are listed in Table 1, showing all regions comprising at least 40 voxels and having *P*-values for individual voxels of at least 0.005. Alertness led to a significantly increased rCBF in the right anterior cingulate (Brodmann area BA 32), in the right middle frontal gyrus (BA 9 and 10), in the brain stem reticular formation at the dorsal ponto-mesencephalic tegmentum, in the right inferior parietal lobulus (BA 40); in the right thalamus, possibly including two structures, one of which can be identified as the pulvinar. The second one is superior, anterior and more lateral to the pulvinar and might be located at the reticular nucleus. Further activations were in the right middle and superior temporal (BA 20, 22) and in the left inferior frontal gyrus (BA 44, 45).

Figure 2a shows the same activated areas superimposed on the average MRI template as transversal slices along the *z*-axis at 4 mm distances. Since due to reconstruction and smoothing the image resolution was rather coarse, Fig. 2b provides a closer look at the sagittal, coronal and transverse slices positioned at the maximum of the brain stem activation. The activated area at the location of the dorsal ponto-mesencephalic tegmentum might comprise the locus coeruleus.

4. Discussion

The results of this simple visual reaction time, intrinsic alertness PET-activation study show involvement of a number of right hemisphere (RH) structures comprising the anterior cingulate, the middle frontal gyrus, the inferior parietal lobulus, the pulvinar and possibly the reticular nucleus of the thalamus, the middle and superior temporal gyrus, and the brain stem reticular formation. The site of the brain stem activation superimposed on the average structural MRI is identical to the right dorsal ponto-mesencephalic tegmentum area reported by Kinomura et al. [14] for a visual RT task and by Paus et al. [25] for an auditory vigilance task with measurement of reaction times. In the Paus et al. study, the mesencephalic region coactivated with the anterior cingulum, the sub-

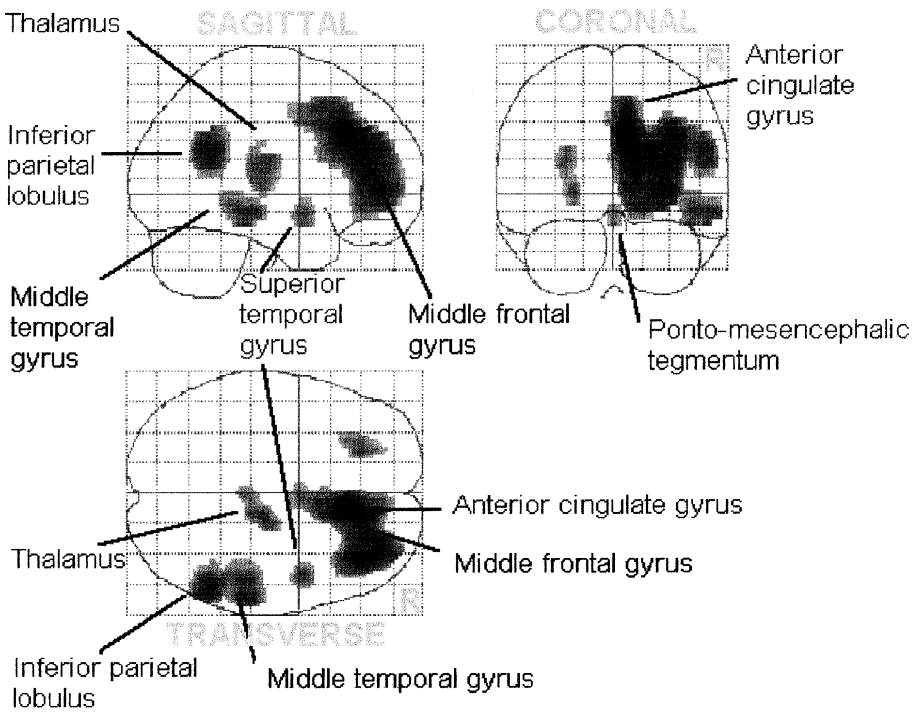

Fig. 1. Comparison of adjusted mean regional cerebral flow (rCBF) in 15 subjects between alertness and a combined sensory and motor control task. Regions comprising at least 40 voxels and having *P*-values of at least 0.005 per voxel are shown as integrated projections along sagittal, coronal and transverse views of the brain (L = left, R = right).

Table 1
ALERTNESS–COMBINED CONTROL. Activated brain areas with Talairach coordinates based on SPM96-analysis showing all regions comprising at least 40 voxels and having *P* values for individual voxels of no more than 0.005

Focus/area		Side	BA*	Talairach coordinates			Region size	*P*-value	*z*-value
				x	*y*	*z*			
1.	Anterior cingulate gyrus	R	32	8	30	32	3035	0.000	5.89
	Middle frontal gyrus	R	9	36	36	32		0.000	4.74
	Middle frontal gyrus	R	10	30	46	4		0.000	4.73
2.	inferior parietal lobulus	R	40	54	−52	24	350	0.000	4.29
3.	Middle temporal gyrus	R	20	60	−28	−12	349	0.000	3.42
4.	Iinferior frontal gyrus	L	44,45	−24	36	0	245	0.001	3.28
5.	Thalamus, possibly reticular nucleus	R		18	−18	20	225	0.001	3.19
	Thalamus, pulvinar	R		12	−22	8		0.001	3.15
6.	Superior temporal gyrus	R	22	46	4	−12	92	0.001	3.12
7.	Dorsal ponto-mesencephalic tegmentum	R		1	−30	−12	49	0.003	2.79

* BA: Brodmann area.

stantia innominata and the thalamus. We are aware that the rather coarse resolution of the SPM does not allow an unequivocal identification of the brain stem structures involved. On the other hand there is evidence that the noradrenergic nuclei located within the region activated in our study and in the studies reported above play a crucial role in alerting. Posner and Petersen [30] propose a right hemisphere noradrenergic (NA) alerting network involving the locus coeruleus as the origin of the NA system [1] as well as frontal areas, but also involving spreading activation to the parietal cortex. Furthermore, the frontal-thalamic gating system, proposed by Stuss and Benson [44] would also seem to be active in alertness activation. The latter authors hypothesize top-down control of the frontal cortex on the reticular nucleus of the thalamus, which, dependent on the 'frontal information', selectively opens thalamic gates for activation originating from the mesencephalic reticular formation. Sustained attention, another aspect of attention intensity, is subserved by RH dorsolateral-frontal and RH superior parietal structures [3, 6, 18, 24].

Combining all these results from the literature with our findings one could postulate a more extended RH network for intrinsic alertness in simple unwarned visual reaction time tasks. This network would involve the right anterior cingulate as well as the right middle frontal gyrus and inferior parietal lobulus, thalamic structures including the pulvinar and possibly the nucleus reticularis and the ponto-mesencephalic tegmentum of the brainstem. This network seems to be involved in supramodal aspects of alertness, since it was also found for an auditory vigilance task [25] and the thalamic and brainstem activation showed up in a somatosensory alertness task [14].

The essential regulating component of this network seems to be the anterior cingulate, which is well known as a center for anticipation and preparation of attentional activity [16, 21]. In a study on auditory vigilance [25] the anterior cingulate activation covaried with activation in the brainstem and the thalamus. Most important, clonidine, an $\alpha 2$ adrenoceptor agonist was shown to decrease activation during a rapid visual information processing task in the superior frontal and inferior parietal cortex while activation in the anterior cingulate increased [8], possibly to counteract the noradrenergic depression caused by clonidine. This lends support to the hypothesis that the anterior cingulate is the frontal structure which modulates the activation of the dorsal noradrenergic bundle [33] probably via the reticular nucleus of the thalamus as proposed in the theory of a frontal-thalamic gating system by Stuss and Benson [44]. This top-down control of the right frontal cortex on noradrenergic activation systems has been demonstrated directly in animal studies. Robinson [38] has shown in the rat that lesions of the right (but not of the left) cerebral hemisphere lead to bilateral depletion of NA and that these depletions are strongest with frontal lesions. Supposed that the ponto-mesencephalic activation of our study and those of Paus et al. [25] and Kinomura et al. [14] would represent the noradrenergic part of this alerting network one could postulate that intrinsic alertness is regulated top-down by the anterior cingulate via the reticular nucleus of the thalamus, which opens the gates of several thalamic nuclei for noradrenergic activation originating in the ponto-mesencephalic tegmentum thus being able to spread through these thalamic nuclei to the middle frontal gyrus and the inferior parietal lobe. This seems to hold true especially for tasks which do not externally trigger alertness phasically, e.g., by a warning stimulus or by a very short interstimulus interval (1 s or less) but which call for a (cognitive) intrinsic control and maintenance of a high level of alertness. Dupont et al. [9] in their PET-study had one condition in which a simple visual detection task calling for fast responses was given at interstimulus intervals of about 1 s. Under this condition there

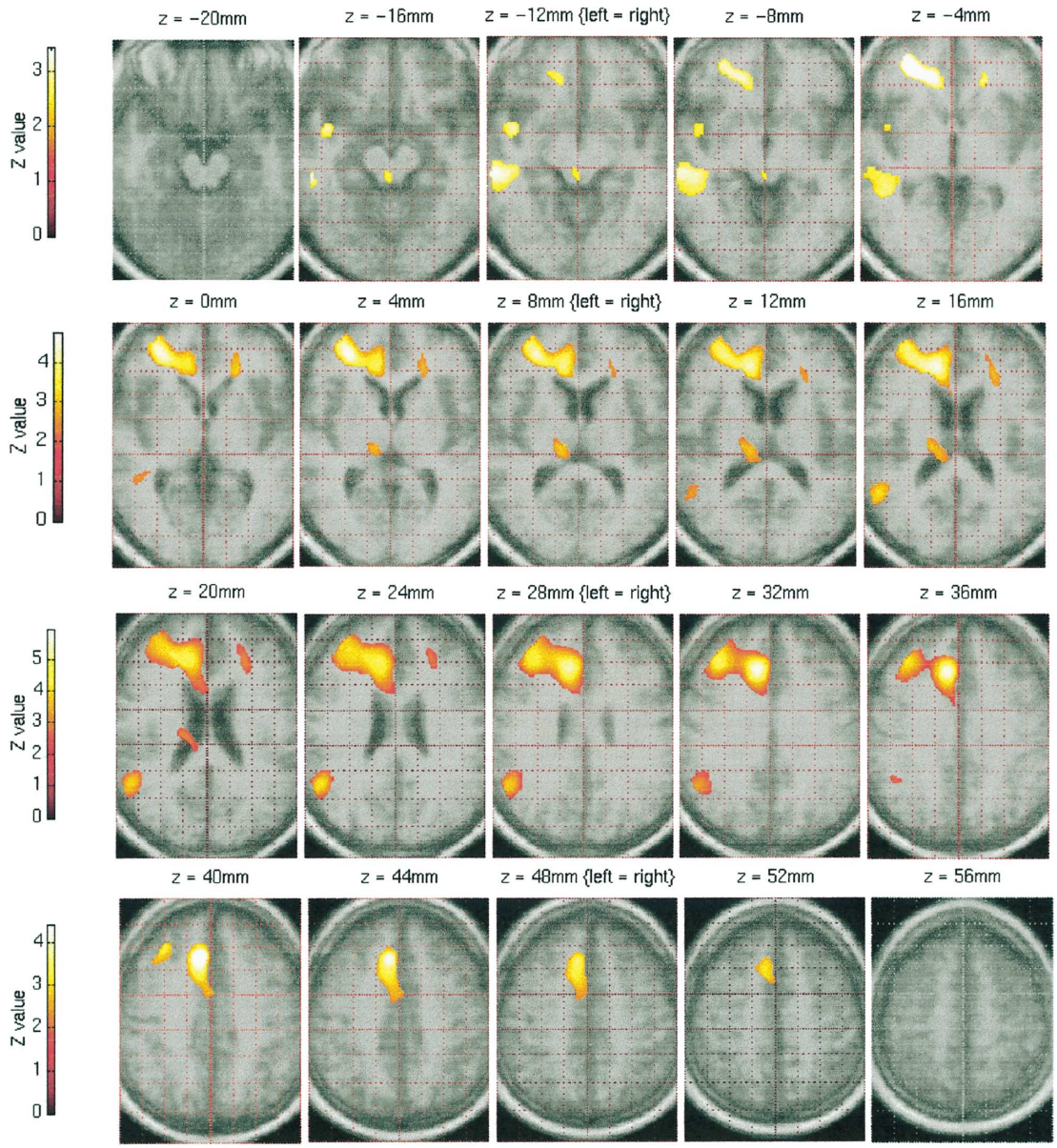

Fig. 2a. Activated areas superimposed on the average MRI template shown as transversal slices along the *z*-axis at 4 mm distances (right hemisphere depicted on the left, left hemisphere on the right side).

even was a decrease of activation in the right frontal, temporal and parietal cortex compared to a passive viewing condition.

All these results might alternatively be interpreted in the opposite direction, i.e., in the sense of a bottom-up, stimulus-driven frontal and parietal activation by brainstem structures. A direct analysis of the direction of this modulation could be accomplished by means of structural equation modelling or path analysis based on activation covariation among brain regions [2] or e.g., by ligand PET studies. On the other hand, both the animal and the pharmacological studies reported above make it highly unlikely that bottom-up modulation is responsible for the frontal and parietal activation observed. We are aware that our study is a purely anatomical one, but we wanted to discuss the results in a little broader perspective taking into account the findings of other studies. Furthermore, our results indicate that both aspects of attention intensity proposed by van Zomeren and Brouwer [48], namely intrinsic alertness and sustained attention seem to share a common right hemisphere frontal and parietal network.

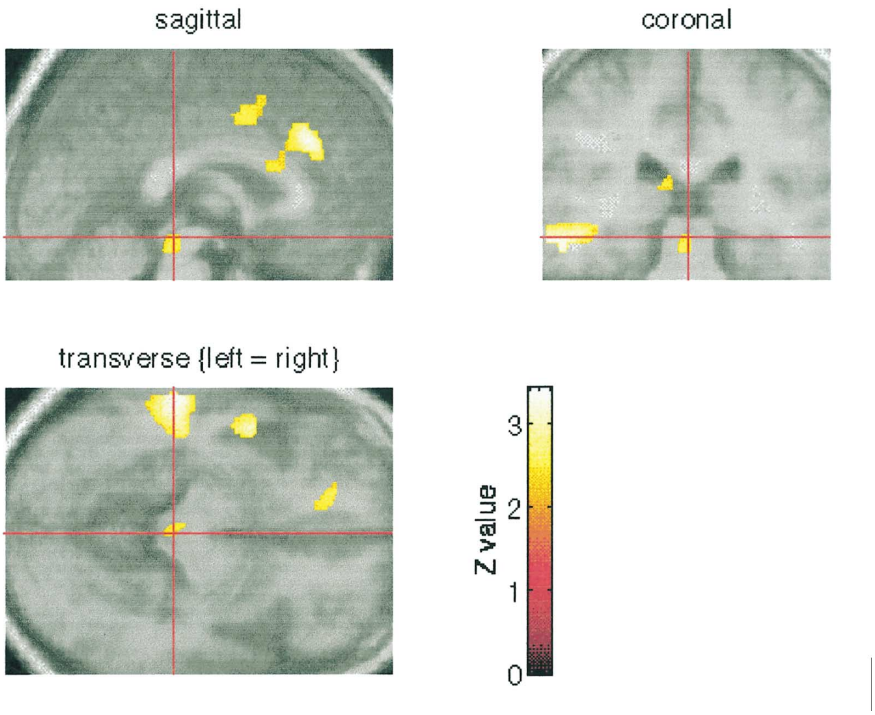

Fig. 2b. Sagittal, coronal and transverse views of the activated area at the location of the dorsal ponto-mesencephalic tegmentum (right hemisphere depicted on the left, left hemisphere on the right side).

Obviously, the right parietal activation found in our study lies inferior to the parietal activation previously reported for sustained attention [24] and is located at a site assumed to be most critical for hemineglect [47]. In a study on the efficacy of a sustained attention training on unilateral neglect the influence of a non-spatial, probably right frontal sustained attention system on the right posterior parietal spatial attention system (as proposed by Posner and Petersen [30]) was demonstrated [35]. The patients—without being trained to compensate directly for their neglect symptoms—showed a significant decrease of symptoms after a self-instruction training aiming at the control of their alertness level. This therapy study lends support to assuming multiple attention systems involving anatomically distinct brain regions which can be co-activated during performance of one attentional task, which holds true for our experiment as well. Again, the direction of this fronto-parietal modulation cannot be inferred directly from our activation data. Nevertheless, the training study by Robertson et al. [35] corroborates Posner and Petersen's [30] hypothesis of a co-activation of the posterior attention system in the parietal cortex involved in spatial orienting of attention by the anterior alerting network, either directly or via the brainstem.

One can, of course, speculate that even in simple reaction time tasks watching a fixation point and looking for relevant stimuli to appear in this location is a spatial attention task per se. This would explain the activation of the inferior parietal cortex and the pulvinar of the thalamus—known to play an outstanding role in engaging and holding attention in a distinct spatial location [26]. LaBerge and Buchsbaum [16] also found a pulvinar activation during recognition and discrimination tasks, i.e., under simple selective attention conditions. This notion was supported in a PET study by Nobre et al. [22]. In a meta-analysis of PET-studies on attention, Shulman et al. [40] pointed out that the common structure that was activated in all studies was the thalamus. An involvement of the thalamus in the regulation of cortical arousal through thalamo-cortical connections which have their origin in dorsomedial, intralaminar and midline thalamic nuclei has been reported earlier e.g., by Montaron and Buser [20]. The role of the intrathalamic interactions involving the reticular nucleus [41, 49] has already been discussed with Stuss and Benson's model of a frontal-thalamic-brainstem top down control of alertness.

The RH temporal activation we found might be unrelated to attentional aspects of the tasks. Instead, it may indicate involvement of the dorsal temporal stream of visual feature extraction [46], since in the alertness condition the white dot has to be discerned from the fixation square, whereas in the combined control condition only the flickering white dot was present at the center of the screen, without a fixation symbol. On the other hand, an activation of the superior temporal sulcus has been reported in a PET-study on spatial shift of attention [22].

In summary, the findings of our study lend support to the hypothesis that simple unwarned visual reaction time tasks calling for both an optimal intrinsically generated level of alertness and its maintenance for extended time periods can lead to the activation of a widespread right hemisphere cortical and subcortical network, which up to now has only been demonstrated in full for an auditory vigilance task involving reaction time measurements over a 60 min time period [25]. The activation of anterior cingulate, thalamic and brainstem structures might represent top down control of frontal cortical on subcortical (possibly noradrenergic) activation systems via the reticular nucleus of the thalamus. In accordance with the studies by Kinomura et al. [14] and by Paus et al. [25] only tasks calling for fast responses without external stimulation by a warning or by short interstimulus intervals acting like a warning seem to be appropriate for eliciting a sufficient level of intrinsic alerting activation to make the rather small brainstem structures 'visible'. Demonstration of an exclusively right hemisphere network, however, can only be expected for very simple stimuli presented repeatedly in an identical way. In tasks with more complex attentional demands, e.g., including selectivity aspects of attention and working memory load this right hemisphere network is involved, too, but additional activations, e.g., in the left hemisphere, will show up. This has been demonstrated by Corbetta et al. [4, 5] for selective and divided attention, by Nobre et al. [22] for visuo–spatial attention, by Dupont et al. [9] for several stages of visual processing and by Coull et al. [7] in a rapid visual information processing task with working memory load.

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